REMARKS

This is responsive to an Office Action mailed on December 13, 2004. In the Office Action the Examiner rejected claims 1, 2, 4-11, 14 and 21-29. Claim 29 is hereby cancelled.

Applicant addresses each rejection in the December 13, 2004 Office Action as follows:

A. Anticipation Rejection of Independent Claim 25 by the Cahalan Patent

The Examiner alleges that the Cahalan U.S. Patent No. 5,308,641 (hereinafter the Cahalan patent) anticipates claim 25 under 35 U.S.C. § 102(b). In the Office Action the Examiner alleged that the Cahalan patent discloses human or animal tissue used as a solid surface and a growth factor. The Examiner also alleged that glutaraldehyde is disclosed as a crosslinking agent at column 4, lines 58-62 and that when glutaraldehyde contacts the solid surface, the glutaraldehyde inherently crosslinks resulting in the crosslinked or fixed tissue as claimed.

Applicant respectfully disagrees with the Examiner that claim 25 is anticipated by the Cahalan patent. An element of claim 25 is associating an exogenous polypeptide growth factor with crosslinked natural tissue. The Cahalan patent does not disclose associating the exogenous polypeptide growth factor with the crosslinked natural tissue.

The Cahalan patent discloses a lightly crosslinked spacer consisting of a polyalkylimine that is attached to a solid surface for the purpose of improving biocompatibility. (Col. 4, lines 14-19). The polyalkylimine is first applied to the solid surface and then is treated with the crosslinking agent. (Col. 6, lines 29-31). The polyalkylimine is reacted with a crosslinking agent where the reaction is completed in a few minutes. (Col. 5, lines 9-10) The crosslinking agent is used to lightly crosslink the polyalkylimine for the purpose of providing a polyalkylimine surface that allows a cellular adhesive molecule or other biomolecules to bond to the spacer. (Col. 4, line 62 – Col. 5, line 3; Col. 6, lines 8-10).

There is no disclosure in the Cahalan patent of a crosslinked natural tissue for association with a polypeptide growth factor. While the Cahalan patent does disclose a crosslinking agent, as the examiner alleges in the office action, the Examiner fails to take into account the portion of the Cahalan patent, following the passage upon which the Examiner relied, that discloses the crosslinking is to be limited to the spacer molecules. The Cahalan patent discloses as follows:

> The spacer of the present invention can therefore be made by applying a polyalkylimine to the solid surface and then **treating the applied polyalkylimine with the cross-linking agent**. Preferably, the cross linking agent used to **crosslink the polyalkylimine** is applied in a dilute solution and at a suitable pH to **accomplish light crosslinking** and to provide functionality for the polyalkylimine surface that will allow biomolecules to readily bond to the spacer.

(Col. 4, line 62-Col. 5, line 3)(Emphasis added). There is no disclosure in the Cahalan patent of a crosslinked natural tissue as is alleged by the Examiner. Rather, the Cahalan patent discloses a lightly crosslinked spacer of polyalkylimine. Polyalkylimine, the only material that is disclosed as being crosslinked in the Cahalan patent, is not a natural tissue. Therefore, the Cahalan patent does not anticipate claim 25.

Contrary to the Examiner's allegation in the Response to Argument section of the Office Action, polyalkylimine is not a natural tissue because it bonds to natural tissue. To make this assertion would lead the examiner to conclude that a titanium plate inserted into a bone would be natural tissue once the bone and the titanium plate bonded. Just as one would not consider titanium to be a natural tissue, polyalkylimine cannot be considered a natural tissue just because it attaches to natural tissue.

Since claim 25 is not anticipated by the Cahalan patent, claim 28 which depends from claim 25 is also not anticipated by the Cahalan patent. Therefore, Applicant respectfully requests that the Examiner withdraw the anticipation rejection of claims 25 and 28 over the Cahalan patent.

B. Anticipation/Obviousness Rejection of Independent Claim 25 Over the Bayne European Patent Application No. 0476983

The Examiner alleges that the Bayne et al. European Patent Application No. 0476983 (hereinafter the Bayne application) anticipates or makes obvious independent claim 25. The Examiner alleges the Bayne application discloses a fibrin coating being applied to or in addition to a VEGF II growth factor to a surface of a fixed umbilical cord vein. The Examiner also speculates (posits) that the tubular supports coated with VEGF II include fixed umbilical cord vein and this anticipates claim 25 where the attachment of the cells to the vessel is done prior to

implantation such that the claim language requiring growth factor associated with the tissue is fully met.

Applicant respectfully disagrees with the Examiner's characterization of the disclosure of the Bayne application. The Bayne application does not disclose a fibrin coating being applied to or in addition to a VEGF II growth factor to a surface of a fixed umbilical cord vein. Rather, the Bayne Application discloses growing cells in a culture in the presence of VEGF II, removing the cells from the culture and plating the cells on fixed umbilical cord vein.

The Bayne Application does not disclose associating an exogenous polypeptide growth factor with crosslinked natural tissue, elements of claim 25. Therefore, the Bayne Application does not disclose each and every element of claim 25. As such the Bayne Application does not anticipate claim 25.

The Examiner also alleged that the Bayne application makes claim 25 unpatentable as being obvious. The Examiner posits (a synonym of assumes) that it would have been clearly obvious to use umbilical cord vein as the tubular support since it is used as an implant in another procedure; it would bring the desired features of tissue properties to the implant site. Furthermore, a combination of proteins such as a fibrin, and growth factor (VEGF II) would have been at least obvious in view of the Bayne Application alone since the teachings of doing the same are all contained in the same paragraph and there is no clear delineation between them.

Applicant respectfully disagrees with the Examiner that claim 25 is obvious over the Bayne Application. The Examiner has failed to meet his initial burden of establishing a *prima facie* case of obviousness.

To establish a *prima facie* case of obviousness, three basic criteria must be met. First, there must be some suggestion or motivation, either in the references themselves or in the knowledge generally available to one of ordinary skill in the art, to modify the reference or to combine reference teachings. Second, there must be a reasonable expectation of success. Finally, the prior art reference (or references when combined) must teach or suggest all the claim limitations. M.P.E.P §2142. The Examiner's assumption used to allege that claim 25 is obvious does not meet the standard for modifying a reference as set forth in case law.

The teaching or suggestion to make the claimed combination and the reasonable expectation of success must both be found in the prior art, and not based on applicant's

disclosure. *In re Vaeck*, 947 F.2d 488, 20 USPQ2d 1438 (Fed. Cir. 1991). The mere fact that references can be combined or modified does not render the resultant combination obvious unless the prior art also suggests the desirability of the combination. *In re Mills*, 916 F.2d 680, 16 USPQ2d 1430 (Fed. Cir. 1990).

Applicant submits that the Examiner used the language of claim 25 as a roadmap to combine aspects of two separate preparation procedures disclosed in the Bayne application for implanting two dissimilar materials, a natural vessel and an artificial vessel. Of note, claim 25 is directed to a prosthetic comprising crosslinked **natural** tissue, therefore the procedure for preparing an **artificial** vessel is not relevant to claim 25. (Emphasis added).

The Examiner combined associating fibrin and growth factor which was disclosed as being coated on an **artificial** vessel with the preparation of a **natural** tissue (fixed umbilical cord vein). However, the Bayne application only discloses coating the **natural** tissue (fixed umbilical cord vein)with endothelial cells prior to implanting. (Emphasis added). There is no reason to combine a method of preparing an **artificial** vessel with a method of preparing a **natural** tissue, absent the present invention, which is impermissible.

The Examiner's reasoning for combining the two separate and dissimilar procedures for preparing dissimilar materials is "the teaching of doing the same are all contained in the same paragraph and there is no clear delineation between them." (Office Action mailed on December 13, 2004, p. 4). A statement that modifies the prior art to meet the claimed invention would have been " 'well within the ordinary skill of the art at the time the claimed invention was made' " because the references relied upon teach that all aspects of the claimed invention were individually known in the art is not sufficient to establish a *prima facie* case of obviousness without some objective reason to combine the teachings of the references. *Ex parte Levengood*, 28 USPQ2d 1300 (Bd. Pat. App. & Inter. 1993). The mere fact that elements of a claim are located in the same reference in proximity to each other does not meet the Examiner's burden for modifying the reference.

Further, Applicant disagrees with the Examiner's characterization of the Bayne Application that the two separate and distinct procedures are not delineated. The Bayne Application at page 8, line 20 starts the sentence with the word "Alternatively." The word

alternatively delineates the first procedure for preparing natural tissue from the second procedure for preparing artificial vessels.

Finally, the Examiner posits (assumes) that since umbilical cord vein is used as an implant in another procedure, it would bring the desired features of tissue properties to the implant site. The Bayne Application discloses how to prepare both a natural vessel (coating with endothelial cells only) and an artificial vessel (coating with proteins such a fibrin and a growth factor (VEGF II)) by distinctly different procedures. There is no teaching in the Bayne Application to combine the two distinctly separate procedures for preparing dissimilar materials for implantation. Therefore, the Bayne Application alone does not make claim 25 obvious.

Since claim 25 is neither anticipated or made obvious by the Bayne Application, claim 26 which depends from claim 25 is also not anticipated or made obvious by the Bayne Application. Therefore, Applicant respectfully requests that the Examiner withdraw the anticipation and obviousness rejections of claims 25 and 26 over the Bayne Application.

C. Obviousness Rejection of Independent Claim 1 Over the Bayne Application In View Of The Wadstrom U.S. Patent No. 5,631,011

The Examiner alleged that the Bayne Application discloses an implant having a fibrin coating (a biologic adhesive as claimed) which is applied prior to the VEGF II growth factor. The Examiner also alleged that fixed umbilical cord vein as disclosed in the Bayne Application is the substrate for coating as claimed. The Examiner alleged that the fixed umbilical cord as disclosed in the Bayne application, while not clearly an allograft or a xenograft, is generic to both. The Examiner finally alleges that it would have been considered clearly obvious to an ordinary artisan to use an allograft or xenograft tissue for the cord vein as disclosed in the Bayne application absent some showing of criticality therefore. The Examiner alleges that the Wadstrom patent discloses that fibrin is a common biologic tissue adhesive in the art and therefore, the fibrin coating as disclosed in the Bayne application would function as a biologic adhesive as claimed.

Applicant respectfully disagrees with the Examiner that claim 1 is obvious over the Bayne application in view of the Wadstrom patent. Elements of claim 1 are a prosthesis for a human patient comprising **allograft or xenograft** tissue having polypeptide growth factor associated therewith. (Emphasis added). An allograft tissue is defined in the specification as

tissue of a different individual of the same species. (Page 8, lines 21-23). A xenograft tissue is defined in the specification as tissue from a species different from the patient's species. (Page 8, lines 19-21). Therefore, allograft tissue and xenograft tissue are natural tissues.

The Examiner again improperly combined the two distinctly separate preparation procedures, one for natural tissue and one for an artificial vessel, disclosed in the Bayne application to improperly allege that the Bayne application discloses coating fixed umbilical cord vein with fibrin and growth factor. Applicant incorporates the arguments made with respect to claim 25 and the Bayne application to show that the Examiner improperly modified the Bayne application and that the Examiner has not met his burden of proving prima facie obviousness.

To reiterate, the Bayne application does not disclose coating fibrin and growth factor on fixed umbilical cord vein. Rather, the Bayne application discloses coating fibrin and growth factor on an artificial vessel. An artificial vessel is neither an allograft tissue nor a xenograft tissue as defined in claim 1. Therefore, the Bayne application does not disclose allograft tissue or xenograft tissue having a polypeptide growth factor associated therewith by a biologic adhesive such as fibrin. Further the Wadstrom patent does not disclose allograft tissue or xenograft tissue having a polypeptide growth factor associated therewith by a biologic adhesive such as fibrin.

The Bayne application in view of the Wadstrom patent does not disclose each and every element of claim 1. Therefore the Bayne application in view of the Wadstrom patent does not make claim 1 obvious. Reconsideration and allowance of claim 1 are respectfully requested.

Claims 2, 4-5 and 9-11 were also rejected as being obvious over the Bayne Application in view of the Wadstrom patent. While Applicant does not acquiesce with the particular rejections to these dependent claims, it is believed that these rejections are moot in view of the remarks made in connection with independent claim 1 above.

For the foregoing reasons the Bayne Application in view of the Wadstrom patent does not make claim 1 obvious. Reconsideration and allowance of claims 1-2, 4-5, and 9-11 are respectfully requested.

D. Obviousness Rejection of Independent Claim 14 Over the Bayne Application In View Of The Wadstrom Patent and The Carpentier Patent.

The Examiner alleged that independent claim 14 is obvious over the Bayne application in view of the Wadstrom patent and the Carpentier patent. The Examiner alleged that the while the

Bayne application fails to disclose uncrosslinked tissue, the heart valve form of tissue, or other types of tissue claimed, the Carpentier patent teaches that all uncrosslinked and crosslinked forms of tissue, heart valve tissue forms and other types of tissue are known in the art. The Examiner then alleges that it would have been obvious to use any of the materials disclosed in the Carpentier patent as the substrate of the Bayne application for the applications contemplated by the Carpentier patent. The Examiner also alleged that one would be motivated to form the implants disclosed in the Bayne application into other shapes to make it useful in other sites and broaden its applicability.

Applicant respectfully disagrees with the Examiner that claim 14 is obvious over the Bayne application in view of the Wadstrom patent and the Carpentier patent. Again, the Examiner improperly modified the Bayne application to combine the distinctly different methods of preparing a **natural** tissue for implantation with the method for preparing an **artificial** vessel for implantation as previously discussed with respect to independent claims 1 and 25.

The Carpentier patent discloses many different **natural** tissues that can be used as heart valve prostheses. (Emphasis added). There is no reason to combine the tissues disclosed in the Carpentier patent with the method of preparation disclosed the Bayne Application for an artificial substrate. "In determining the propriety of the Patent Office case for obviousness in the first instance, it is necessary to ascertain whether or not the reference teachings would appear to be sufficient for one of ordinary skill in the relevant art having the reference before him to make the proposed substitution, combination, or other modification." *In re Linter*, 458 F.2d 1013, 1016, 173 USPQ 560, 562 (CCPA 1972).

The tissue disclosed in the Carpentier patent is natural tissue. As such, the tissue disclosed in the Carpentier patent as applied to the disclosure of the Bayne application would be prepared by plating cells that were grown in vitro in a VEGF II solution, and then the tissue would consequently be implanted into the patient.

The combination of the Bayne application with the Carpentier patent would not provide a natural tissue heart valve comprising a substrate associated with VEGF. Therefore, the Bayne application in view of the Wadstrom patent and the Carpentier patent does not make claim 14 obvious.

Further, the Examiner improperly used the invention defined in claim 14 as a roadmap to allege obviousness. Claim 14 defines the present invention as a prosthetic heart valve. The Examiner cites the Bayne application as the primary reference. However, the Bayne application does not disclose the implanting of a heart valve, rather the preparation of artificial and natural blood vessels for implantation.

In fact, when this issue was addressed in the previous amendment, the Examiner responded that the motivation to combine the references was"[o]ne would be motivated to form Bayne et al implants into other shapes in order to make it useful in other sites and broaden its applicability." (See Office Action mailed on December 13, 2004, p. 9). The Examiner's stated purpose for combining the Bayne application with the Carpentier patent is an improper combination.

"There are three possible sources for a motivation to combine references: the nature of the problem to be solved, the teachings of the prior art, and the knowledge of persons of ordinary skill in the art." *In re Rouffet,* 149 F.3d 1350, 1357, 47 USPQ2d 1453, 1457-58 (Fed. Cir. 1998). Broadening the applicability of a reference beyond its disclosure is not a permissible reason to combine references. As such, the combination of the Bayne application with the Carpentier patent is an improper combination.

Finally, the Examiner states that the Bayne application is drawn to all types of vascular tissue repair. The Examiner then alleges that tissue heart valves are a type of vascular graft. (See Office Action mailed on December 13, 2004, p.9). However, a definition of a vascular graft is "tube replacement of an artery or vein segment". Joseph D. Branzino, The Biomedical Engineering Handbook, Second Edition, Vol. II, p. 128-8, CRC Press (2000). (Exhibit A). Thus, a heart valve prosthesis does not fall within the definition of a vascular graft. Therefore, the Examiner has improperly stated that heart valve implants (cardiac implants) are vascular grafts and cannot equate a disclosure for a blood vessel implant with a heart valve prosthetic.

For the foregoing reasons, claim 14 is not made obvious over the Bayne application in view of the Wadstrom patent and the Carpentier patent. As such, reconsideration and allowance

of claim 14 are respectfully requested.

Claims 6-8 depend from independent claim 1, claims 15 and 21-24 depend from independent claim 14, and claims 27-28 depend from independent claim 25. While Applicant does not acquiesce with the particular rejections to these dependent claims, it is believed that these rejections are moot in view of the remarks made in connection with independent claims 1, 14, and 25 above.

E. Double Patenting Rejection

In response to the Examiner's double patenting rejection, Applicant submits that it may file a terminal disclaimer in the event that both the present application and copending application 09/186,810 issue into patents.

Conclusion

Applicant believes that the present application is in condition for allowance. Applicant respectfully requests that claims 1, 2, 4-11, 14, 15 and 21-28 be reconsidered and allowed.

The Director is authorized to charge any fee deficiency required by this paper or credit any overpayment to Deposit Account No. 23-1123.

Respectfully submitted,

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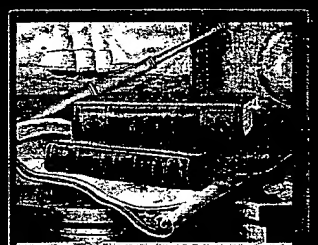

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Neointimal hyperplasia: Fibroblast and smooth-muscle cell growth covering a vascular graft on the inside surface.

Pannus: Neointimal hyperplasia tissue ingrowth at the anastomoses.

Pseudointimal hyperplasia: Fibrin/thrombin deposition on the inside surface of an arterial vascular graft. This accumulation of material is acellular.

Stenosis: Tissue ingrowth into vessel causing a narrow lumen and reduction of blood flow.

Vascular graft: Tube replacement of an artery or vein segment.

Vascular reconstruction: Reconstruction of an artery or vein after trauma, surgery, or blockage of blood flow from disease.

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Further Information

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